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13. ABSTRACT *(Maximum 200 Words)*

Cowden syndrome (CS) is an autosomal dominant disorder charcterized by multiple hamartomas and a high risk of breast, thyroid and other cancers. The susceptibility gene is PTEN. The edict of this grant is to determine the genetic role of PTEN in non-CS CS-like families or individuals. The PI has accrued 15 site specific breast cancer families, without known BRCA1 and BRCA2 mutations. No intragenic PTEN mutations were found in these families. To date, 70 CS-like families and individuals have been accrued. One occult germline PTEN intragenic mutation was found among these families. The mutation positive family has breast, thyroid and endometrial cancers. Unfortunately, only 5 other families have endometrial carcinoma. In summary, at least 1.5% of non-CS CS-like families carry occult PTEN mutations. This has implications for the proband and family with respect to cancer risk and surveillance. Our preliminary data may suggest that endometrial cancer is a true component of CS and the data suggests that the International Cowden Consortium clinical diagnostic criteria are robust. Further accrual of these CS-like families, enriching for endometrial cancer, will be achieved and PTEN analysis, including the promoter, pursued.

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FOREWORD

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Introduction

Cowden syndrome (CS) is an autosomal dominant disorder characterized by multiple hamartomas and a high risk of breast, thyroid and other cancers (reviewed by Eng [1]). The risk of breast cancer in affected women can range from 25-50% [2,3]. The PI mapped the *CS* gene to 10q22-23 [4] and subsequently identified *PTEN*, encoding a dual specificity phosphatase, as the or at least a major CS susceptibility gene [5]. That *PTEN* is a major CS gene was subsequently confirmed by other groups [6-8]. In addition, the PI has shown that germline *PTEN* mutations cause a proportion of Bannayan-Riley-Ruvalcaba syndrome (BRR), an autosomal dominant disorder characterized by megencephaly, mental retadartion, lipomatosis, and speckled penis, previously thought not to be associated with cancer [9].

Because CS is difficult to diagnose and is under-recognized and therefore under-diagnosed, the PI chairing the International Cowden Consortium synthesized a set of diagnostic criteria for the operational diagnosis of CS (Table 1) [10], initially for research purposes and now, for clinical diagnostic purposes as well.

Table 1. International Cowden Consortium Diagnostic Criteria for CS

<u>Pathognomonic Criteria</u>

Mucocutanous lesions:

- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

<u>Major Criteria</u>

Breast CA
Thyroid CA, esp. follicular thyroid carcinoma
Macrocephaly (Megalencephaly) (say, $\geq$97%ile)
Lhermitte-Duclos disease (LDD)

<u>Minor Criteria</u>

Other thyroid lesions (e.g adenoma or multinodular goiter)
Mental retardation (say, IQ $\leq$75)
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
GU tumors (eg uterine fibroids) or malformation

<u>Operational Diagnosis in an Individual</u>:

1. Mucocutanous lesions alone if:

a) there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
b) cutaneous facial papules and oral mucosal papillomatosis, or
c) oral mucosal papillomatosis and acral keratoses, or

d) palmo plantar keratoses, 6 or more
2. 2 Major criteria but one must include macrocephaly or LDD
3. 1 Major and 3 minor criteria
4. 4 minor criteria

Operational Diagnosis in a Family where One Individual is Diagnostic for Cowden
1. The pathognomonic criterion/ia
2. Any one major criterion with or without minor criteria
3. Two minor criteria

The question of "cryptic" CS or the frequency of mutation-proven CS in individuals or families presenting with components of CS, such as breast cancer and/or thyroid cancer and/or endometrial cancer is important for the patient and his/her family with regard to medical management. In this regard, this proposal asks two main questions:

Task 1: What proportion of familial breast cancer only families have CS?

Task 2: What proportion of CS-like families, which do not make the full diagnostic criteria of the International Cowden Consortium (Table 1) have germline *PTEN* mutations, with its full implications, targeting cases and families that have breast and/or thyroid/endometrial cancer.

Body

Task 1: Germline *PTEN* mutations in breast cancer only families
To date, a total of 15 site specific breast cancer families that are mutation negative for *BRCA1* and *BRCA2* have been accrued and documented. All 15 are germline *PTEN* mutation negative. Approximately half of the afftected tested individuals are heterozyous at *PTEN* IVS8+32T/G, thus excluding whole gene deletion. At this point, there is extensive data to show that gross gene deletion only results in BRR and even then, it is rare [11]. Again, all this analysis has been performed from small amounts of DNA left from old samples used for *BRCA* searches or from paraffin-embedded archived material, thus making Southern analysis impossible on these particular samples.

The plans for Years 2 and 3 is to continue accrual of site specific breast cancer families without *BRCA1* and *BRCA2* mutations for PCR-based germline *PTEN* analysis. These hopefully will be from peripheral blood leucocytes, thus making Southern analysis possible. The promoter lies within or is 250 kb long. Efforts by our lab and other labs are beginning to determine which portion or all of this segment is the minimal "true" promoter. If feasible after these analyses, then promoter mutation analysis will be performed in these families as well.

It would also appear from recent data (from our lab and others) that PTEN can be silenced or "inactivated" by causes other than structural gene alteration (ie mutation or deletion) (eg, Dahia et al 1999 [12]). In this regard, the PI plans to extend Task 1 to include examination of PTEN expression using immunohistochemistry to delineate

whether structural and/or other epigenetic phenomena pertain in PTEN inactivation in breast carcinogenesis.

Task 2: Mutation Analysis in Non-CS Breast-Thyroid and/or Endometrial Carcinoma Families/Individuals ("CS-Like Families")

To date, a total of 70 individuals or families with a CS-like syndrome have been accrued and cancers and tumors in affected individuals have been documented either with pathology report (preferable), death certificate or physician's notes. Each of these cases or families does not meet the operational diagnostic criteria for CS (Table 1). Further, they must minimally have at least one member with nonmedullary thyroid carcinoma and at least one other related member with breast cancer diagnosed at any age. They could also comprise single cases with both nonmedullary thyroid tumor and breast cancer. Among these 70 families/individuals, 1 germline *PTEN* mutation, c.209T->C (exon 3), was detected [13] (unpublished data). This was detected in a family where the proband was diagnosed with follicular thyroid carcinoma at the age of 31 and his mother had breast carcinoma diagnosed at 49 and 53, respectively, and endometrial carcinoma at 63. Half of these families/individuals were heterozygous at IVS8+32T/G thus excluding whole gene deletion. We and others have also shown that in CS and even BRR, whole gene deletion is rare [5,7,9,11,14,15]. Indeed, if *PTEN* is grossly deleted, only the BRR phenotype results [11]. Therefore, for the moment, the PI has decided that further hemizygote analysis on the large scale is not cost-efficient nor scientifically warranted.

From this Year 1 analysis, it would appear that the endometrial cancer feature in CS-like cases and families might increase the likelihood of finding a germline *PTEN* mutation. Therefore, while accrual of further CS-like families will continue, the PI will target families with endometrial pathology for Years 2 and 3. Southern analysis must await further accrual as amount of DNA per sample is limited with much of the analyses of these first 70 occurring off DNA templates extracted from paraffin-embedded archival material. Although promoter analysis was proposed in the original SOW, the promoter is within a 250 kb segment. We and others are trying to determine if the true promoter may be within a more confined region before beginning genetic analyses – this strategy would be meaningful.

Key Research Accomplishments

Task 1

- Clinical-genetic database being set up

Task 2

- Clinical-genetic database of CS-like families being set up
- Delineate the frequency of occult germline *PTEN* mutation in CS-like families and individuals
- Discovered that based on molecular data, the clinical operational diagnostic criteria for classic CS is robust
- Based on the findings thus far, the PI as Chair of the International Cowden Consortium has recommended that endometrial carcinoma be added to the list of major criteria in the operational diagnosis of CS (see Table 1 for 1995 Criteria). This is the first data-based update of criteria since 1995. The US NCCN/Genetic-High Risk Panel has agreed to adopt this revision in their 2000 guidelines.

Reportable Outcomes

Marsh DJ, Dahia PLM, Caron S, Kum JB, Frayling IM, Tomlinson IPM, Hughes KS, Hodgson SV, Murday VA, Houlston R, **Eng C**. Germline *PTEN* mutations in Cowden syndrome-like families. J Med Genet 1998; 35:881-5.

Conclusions

In Year 1 of the grant, the PI has continued to accrue non-CS families and individuals. A clinical-genetic database is actively being built. It is envisioned that this will be on-going for the next 2 years. Because of the PI's disruptive move from Boston in the beginning of the year, the database assistant is just being hired (the PI herself was manually inputting and analyzing data). Nonetheless, in the first analysis of non-CS CS-like families and individuals, the PI has found approximately 1.5-2% with an occult germline *PTEN* mutation. Re-examination of the family has found that they have breast, thyroid and endometrial cancer and no other stigmata of CS. Thus, the PI preliminarily concludes that the Clinical Operational Criteria for CS Diagnosis proposed by the International Cowden Consortium is robust, and that perhaps, endometrial carcinoma should be added to the list of major criteria.

In order to confirm these early findings, the PI will continue to accrue such CS-like families and individuals but to enrich for endometrial cancer or non-neoplastic endometrial disease (eg young onset endometrial fibroids can be a feature of CS). Germline *PTEN* mutation analysis will be pursued and the promoter elucidated and finally examined for alterations.

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Appendix

Marsh DJ, Dahia PLM, Caron S, Kum JB, Frayling IM, Tomlinson IPM, Hughes KS, Hodgson SV, Murday VA, Houlston R, **Eng C**. Germline *PTEN* mutations in Cowden syndrome-like families. J Med Genet 1998; 35:881-5.

Original articles

Germline PTEN mutations in Cowden syndrome-like families

Debbie J Marsh, Patricia L M Dahia, Stacey Caron, Jennifer B Kum, Ian M Frayling, Ian P M Tomlinson, Kevin S Hughes, Rosalind A Eeles, Shirley V Hodgson, Vicky A Murday, Richard Houlston, Charis Eng

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Abstract
Cowden syndrome (CS) or multiple hamartoma syndrome (MIM 158350) is an autosomal dominant disorder with an increased risk for breast and thyroid carcinoma. The diagnosis of CS, as operationally defined by the International Cowden Consortium, is made when a patient, or family, has a combination of pathognomonic major and/or minor criteria. The CS gene has recently been identified as PTEN, which maps at 10q23.3 and encodes a dual specificity phosphatase. PTEN appears to function as a tumour suppressor in CS, with between 13-80% of CS families harbouring germline nonsense, missense, and frameshift mutations predicted to disrupt normal PTEN function. To date, only a small number of tumour suppressor genes, including BRCA1, BRCA2, and p53, have been associated with familial breast or breast/ovarian cancer families. Given the involvement of PTEN in CS, we postulated that PTEN was a likely candidate to play a role in families with a "CS-like" phenotype, but not classical CS. To answer these questions, we gathered a series of patients from families who had features reminiscent of CS but did not meet the Consortium Criteria. Using a combination of denaturing gradient gel electrophoresis (DGGE), temporal temperature gel electrophoresis (TTGE), and sequence analysis, we screened 64 unrelated CS-like subjects for germline mutations in PTEN. A single male with follicular thyroid carcinoma from one of these 64 (2%) CS-like families harboured a germline point mutation, c.209T→C. This mutation occurred at the last nucleotide of exon 3 and within a region homologous to the cytoskeletal proteins tensin and auxilin. We conclude that germline PTEN mutations play a relatively minor role in CS-like families. In addition, our data would suggest that, for the most part, the strict International Cowden Consortium operational diagnostic criteria for CS are quite robust and should remain in place.
(*J Med Genet* 1998;35:881–885)

Keywords: PTEN; Cowden syndrome; breast; thyroid

Breast and thyroid carcinoma are two frequently occurring neoplasms in the female population. Increased risks for both breast and thyroid cancer are prominent features of Cowden syndrome (CS). The hallmark phenotype of this inherited cancer syndrome is the presence of hamartomas, developmentally incorrect, benign, hyperplastic growths, in multiple organ systems including the skin, gastrointestinal tract, central nervous system, breast, and thyroid. Breast cancer will develop in 25-50% of women with CS and 3-10% of all CS patients will develop thyroid cancer.[1 2] At present, only four tumour suppressor genes have been associated with familial breast cancer, BRCA1, BRCA2, p53, and PTEN.[3-7] Initially thought to account for over 80% of hereditary breast cancer,[8 9] germline mutations in BRCA1 and BRCA2 together are now thought to account for 25-50% of all familial breast cancer,[10] thus opening up the possibility of other BRCAX genes. Along these lines, germline mutations in p53 are associated with 70% of cases of Li-Fraumeni syndrome, an autosomal dominant condition comprising breast cancer, brain tumours, sarcomas, and adrenocortical carcinomas.[3 4 11] Recently, the CS susceptibility gene has been identified as the tumour suppressor gene PTEN, also known as MMAC1 and TEP1.[7 12-14] PTEN maps to 10q23.3 and encodes a 403 amino acid dual specificity phosphatase.[12-15] Germline missense and truncating mutations have been reported in between 13-80% of patients with CS.[7 16-18] It should be noted that while initial linkage studies of 12 families with CS was highly suggestive of a single locus for CS,[19] a subsequent study proposes that genetic heterogeneity may exist in CS.[16]

At the somatic level, PTEN has been shown to be mutated or deleted in a number of human malignancies, including sporadic breast, brain, prostate, and kidney cancer cell lines, as well as in a number of primary tumours including endometrial carcinomas, glioblastomas, malignant melanoma, and thyroid and breast tumours.[20-33]

Given the role of PTEN in CS and the relatively large percentage of familial cases of breast cancer that are not caused by germline mutation of BRCA1, BRCA2, or p53, we sought to determine whether PTEN may be mutated in

Table 1 Phenotypic classification of CS-like families

Phenotype of families	*No of families*
Breast and thyroid carcinoma occurring together in at least one person	22
Breast and thyroid carcinoma occurring in different subjects	32
Breast carcinoma and thyroid disease (eg goitre)	3
Breast carcinoma/CS-like (eg trichilemmoma), no thyroid involvement	6
Thyroid carcinoma/CS-like, no breast involvement	1
Total	64

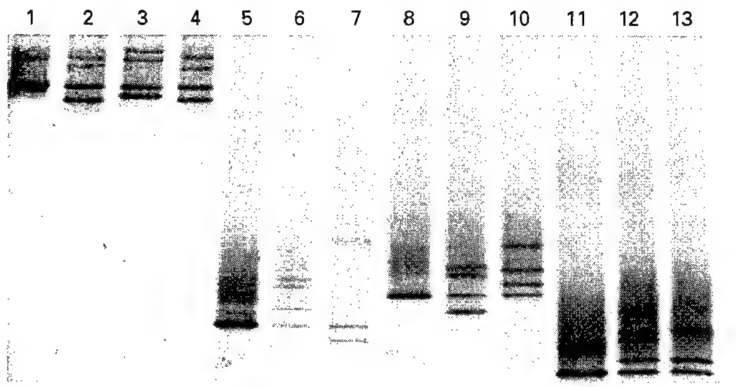

Figure 1 DGGE detection of c.209T→C in the germline of a patient from a CS-like family. Control mutations from CS and BRR families are also included to display the sensitivity of this technique for the detection of PTEN mutations. Lane 1, wild type control (exon 3); lane 2, Y68H (exon 3); lane 3, IVS2-2A→G (exon 3); lane 4, c.209T→C (exon 3); lane 5, wild type control (amplicon 5I, representing the 5' half of exon 5); lane 6, Q87X (amplicon 5I); lane 7, c.347-351delACAAT (amplicon 5I); lane 8, wild type control (amplicon 5II, representing the 3' half of exon 5); lane 9, C124R (amplicon 5II); lane 10, E157X (amplicon 5II); lane 11, wild type control (exon 7); lane 12, R233X (exon 7); lane 13, c.791ATins (exon 7).

the germline of families that did not meet the strict diagnostic criteria for CS determined by the International Cowden Consortium.[2 19] The phenotypes of these families were, minimally, breast and non-medullary thyroid cancers, and, maximally, a sum of phenotypes falling just short of the Consortium Criteria for CS.

Material and methods

PATIENTS

Members of 64 unrelated CS-like families were collected for analysis (table 1). These CS-like families were defined as families or people that have some, but not all, of the features of CS and do not meet the operational diagnostic criteria of the International Cowden Consortium. Minimally, these CS-like families contained at least one member with both non-medullary thyroid cancer and at least one other related member with breast cancer diagnosed at any age. They also could comprise subjects with both breast cancer and non-medullary thyroid cancer. Alternatively, families could be made up of either breast or non-medullary thyroid cancer and other features of CS, such as trichilemmomas, without meeting the consortium criteria for CS.

The diagnostic criteria for classical CS used in this study has been previously described by the Consortium.[2 19] In brief, the diagnosis of CS requires that a patient or family meet a combination of pathognomonic major and minor criteria. Major criteria include breast cancer, non-medullary thyroid cancer (especially follicular thyroid carcinoma), macrocephaly (≥97th centile), and Lhermitte-Duclos disease (LDD), which is a dysplastic gangliocytoma of the cerebellum that can cause seizures, tremors, and poor coordination. Hamartomas of the skin, including trichilemmomas (benign tumours of the hair follicle infundibulum) and mucocutaneous papillomatous papules (for example, scrotal tongue), are diagnostic if there are six or more papules, with three or more being trichilemmomas. Minor criteria include benign thyroid lesions such as multinodular goitre and adenomas, fibrocystic breast disease, mental retardation (IQ≤75), gastrointestinal hamartomas, lipomas, fibromas, and genitourinary tumours or malformations. Individual people or families would be diagnosed with CS if they have two major criteria, where one is either LDD or macrocephaly, one major with three minor criteria, or four minor criteria. No patients in this study fulfilled these criteria. Constitutional DNA was extracted from blood leucocytes using standard, previously described methods.[34] Approval for the use of human subjects in this study was obtained under IRB approved protocol 94-138 (Dana-Farber Cancer Institute).

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DENATURING GRADIENT GEL ELECTROPHORESIS (DGGE) AND TEMPORAL TEMPERATURE GEL ELECTROPHORESIS (TTGE)

A combination of DGGE and TTGE was performed for all nine exons of PTEN. GC clamped primer sequences, PCR conditions, and DGGE conditions have been previously described,[35] with the exception of primers for exons 2 and 4. Exon 2 and 4 primer sequences, with GC clamps added, were as follows: exon 2, 2F, 5'-CGT CCC GCG TTT GAT TGC TGC ATA TTT CAG-3' and 2R, 5'-CGC CCG CCG CGC CCC GCG CCC GTC CCG CCG CCC CCG CCC GTC TAA ATG AAA ACA CAA CAT G-3'; exon 4, 4F, 5'-CGC CCG CCG CGC CCC GCG CCC GTC CCG CCG CCC CCG CCC GAA ATA ATA AAC ATT ATA AAG ATT CAG GCA ATG-3' and 4R, 5'-GAC AGT AAG ATA CAG TCT ATC-3'. Split exon 5 primers with GC clamps and conditions for mutation detection have been previously reported.[26]

TTGE is a mutation detection technique using the basic PCR fragment denaturation principles of DGGE. The major difference between these methods is that a temperature gradient, rather than a chemical gradient of varying urea and glycerol percentages, is used for strand separation of the GC clamped homo- and heteroduplexed PCR products by generating a linear temperature gradient over the length of the electrophoresis run (Bio-Rad Laboratories, Hercules, CA). One or 0.75 mm thick gels of 10% polyacrylamide:bis (37.5:1) (Bio-Rad Laboratories) and 7 mol/l urea (Bio-Rad Laboratories) were run using the DCode™ Universal Mutation Detection System (Bio-Rad Laboratories). Electrophoresis was performed at 130 V for six hours with a temperature gradient of 46-58°C and a ramp rate of 2°C per hour. TTGE fragments were visualised under ultraviolet transillumination after the gel was stained with ethidium bromide (Bio-Rad Laboratories).

Both DGGE and TTGE have proven high accuracy in detecting mutations in general and specifically in detecting known PTEN mutations from CS patients (fig 1).

SEQUENCE ANALYSIS

Exons which showed DGGE and TTGE variants underwent direct sequence analysis. The PCR primers and reaction conditions have been described elsewhere.[7,14,28,35] PCR products were gel isolated and purified using the Wizard PCR Preps DNA Purification System (Promega, Madison, WI). Direct sequencing of these products was performed using the ABI Prism dye terminator cycle sequencing ready reaction kit (Perkin-Elmer Corp. Norwalk, CT). Cycle sequencing products were electrophoresed on 6% Long ranger gels (FMC Bioproducts, Rockland, ME) and analysed on an Applied Biosystems model 373A automated DNA sequencer (Perkin-Elmer Corp).

PTEN POLYMORPHISM ANALYSIS

A previously identified intronic polymorphic site in PTEN, IVS8+32G/T, was analysed in a single affected member from each CS-like family to investigate hemizygosity at the PTEN locus in mutation negative families. This site is moderately heterozygous, with an earlier report finding 50% of samples to be informative.[28] Potential hemizygosity was assessed by the amplification of exon 8 and flanking intronic sequence and digestion with the restriction endonuclease *Hinc*II under conditions suggested by the manufacturer (New England Biolabs, Beverly, MA).

Results

PTEN MUTATION ANALYSIS

A missense point mutation, c.209T→C (L70P), predicted to affect splicing was identified in a single affected patient (1 of 64, 2%) (fig 1). This mutation was not identified in 100 normal alleles. When this occult germline PTEN mutation was identified, the family history was reassessed (fig 2). The subject analysed for this study, III.1, developed follicular thyroid carcinoma at the age of 31. His mother, II.2, had breast adenocarcinoma diagnosed at the age of 49 and again at 53. She also had endometrial carcinoma diagnosed at 63 years. Careful clinical assessment of these two subjects was unable to identify macrocephaly, skin lesions typical of CS, or scrotal tongue. The maternal grandfather, I.1, was diagnosed with leukaemia at the age of 57. Unfortunately, family members other than III.1 were unavailable for analysis. Fresh tumour from III.1, which would have allowed us to study the putative aberrant splicing effect of this mutation, was also unavailable. No mutations were identified in the other 63 unrelated CS-like families.

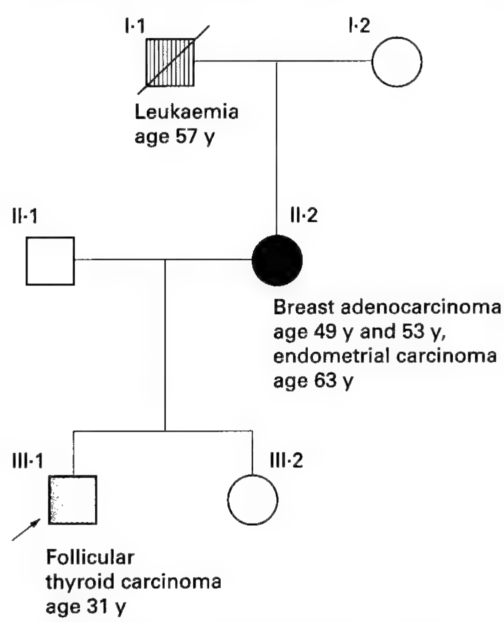

Figure 2 Pedigree of CS-like family with the occult germline PTEN mutation. c.209T→C was identified in DNA extracted from blood leucocytes from patient III.1 who presented with follicular thyroid carcinoma.

PTEN POLYMORPHISM ANALYSIS

Forty-eight percent (30 of 63) of unrelated subjects from PTEN mutation negative CS-like families were found to be heterozygous at the IVS8+32T/G site. This analysis would suggest that, at least in these families, gross germline deletion of PTEN can be excluded.

Discussion

An occult germline PTEN mutation, c.209T→C at the last nucleotide of exon 3 was found in one of 64 (2%) CS-like families. This family's cancers, comprising leukaemia, which may or may not be related, adenocarcinoma of the breast, endometrial carcinoma, and follicular thyroid carcinoma, together do not meet the International Cowden Consortium Criteria used for the diagnosis of CS in this study. However, we cannot exclude the possibility that this family represents a case of low penetrance CS. The family with PTEN mutation in this study contrasts with that in a recent study that reported a PTEN mutation in a family initially classified as having breast and thyroid tumours only but reclassified as CS after mutation analysis led to closer clinical assessment.[36] Closer clinical assessment of the family presented in the current study did not identify additional features of CS.

In the remaining families where no occult germline mutations were identified, it is highly unlikely that these mutations would have gone undetected. Both DGGE and TTGE are highly sensitive mutation detection techniques[37] and both have been shown consistently to detect known PTEN mutations and other sequence polymorphisms (Marsh and Eng, unpublished data, 1998; fig 1). Further, because at least one affected member from nearly half of these mutation negative families was heterozygous at the IVS8+32T/G polymorphism, whole gene deletion is unlikely, at least in these families.

In CS, while missense and truncating mutations are scattered largely along the entirety of PTEN, a mutational "hot spot" exists in exon 5, which contains the PTPase core motif at codons 122-132.[7,16-18] Thus, many mutations in CS are predicted to disrupt the phosphatase function of this protein. Interestingly, the mutation identified in exon 3 falls in the N-terminal half of the PTEN protein that has been shown to have some sequence similarities to the cytoskeletal proteins tensin and auxilin.

Specifically, the leucine residue at codon 70 that is altered by this T to C point mutation (L70P) is conserved in both bovine auxilin and chicken tensin.[14] Thus, it is possible that this mutation may be affecting the phosphatase function of this protein, as one may predict if this putative splice site mutation leads to a truncated protein, and may also function to disrupt normal cellular motility and cell-cell interactions.

Whether germline PTEN mutations are associated with CS and related inherited hamartoma syndromes (Bannayan-Ruvalcaba-Riley syndrome, (BRR, MIM 153480) and juvenile polyposis syndrome (JPS, MIM 174900)), as well as syndromes comprising partial CS phenotypes, is largely unknown. Before the identification of PTEN as the CS gene, it was not inconceivable that the three related hamartoma syndromes and CS-like syndromes were all associated with different mutations in a single gene. We have shown that germline PTEN mutations are associated with the great majority, approximately 80%, of classical CS families.[7 18] Nelen *et al*[17] identified PTEN mutations in 47% of CS cases studied. One other study of 23 CS families identified only 13% of families with germline PTEN mutation.[16] This was perhaps not surprising as limited linkage information in these families suggested the possibility of genetic heterogeneity in CS, even though initial studies of a group of 12 CS families showed no evidence for heterogeneity.[19]

We have also shown that germline PTEN mutations account for at least a proportion of BRR, which is characterised by macrocephaly, lipomatosis, thyroid dysfunction, hamartomatous polyps of the gastrointestinal tract, and pigmented macules of the glans penis, but without a known predisposition to breast and thyroid cancer.[18 38] How mutations in a single gene, at times identical,[18 38] can function to predispose to two overlapping but apparently distinct syndromes, one with malignancy and one without, remains to be elucidated.

Disparate reports concerning the third hamartoma syndrome, JPS, and PTEN mutation or deletion have recently been published.[35 36 39-41] A putative JPS locus, JP1, at 10q22-24 was initially thought to encompass PTEN, although fine structure mapping placed this locus slightly centromeric of PTEN.[42] Subsequently, the 10q22-24 region was excluded as a putative JPS locus by linkage analysis in eight JPS families.[35] Screening of PTEN in 21 classical JPS families and 16 cases of sporadic JPS did not identify any germline mutations.[35 39] In contrast, PTEN mutation has been reported in four patients with "juvenile polyposis",[36 41] although the clinical diagnosis of classic juvenile polyposis in these cases is questionable. Given these genetic data and the phenotypic overlap of these syndromes, we can say with some confidence that if a germline PTEN mutation were detected in a person previously thought to have "juvenile polyposis", then the diagnosis needs to be revised, as that person is likely to have either CS or BRR.

Along the same lines, we have now investigated a cohort of families, each of which contains some of the component tumours of CS but do not meet the Consortium diagnostic criteria for CS. Only one such family was found to have an occult germline PTEN mutation, arguing that such germline alterations play a minor role in families that do not meet the strict CS diagnostic criteria. Nonetheless, this finding is significant for three reasons. Firstly, it suggests that the operational diagnostic criteria for CS established by the International Cowden Consortium are, for the most part, robust and are useful for identifying PTEN mutation positive CS families. Secondly, we must also conclude from our data that other genes are involved which lend susceptibility to a CS-like disease and to site specific breast and non-medullary thyroid cancer. Thirdly, for non-CS subjects identified with occult PTEN mutations, albeit uncommonly, there are important implications for future hamartoma/cancer development that should impact on surveillance.

Unanswered questions remain, however. For example, are CS-like families without germline PTEN mutations at any less risk of cancer than those with mutations? Preliminary genotype-phenotype analyses suggest that classical CS families without germline PTEN mutations are at lower risk of developing malignant breast disease compared to their PTEN mutation positive counterparts.[18] By extrapolation, it would seem that PTEN mutation negative CS-like families should be at decreased risk of developing breast cancer. Unfortunately, this study was unable to confirm this clinically relevant extrapolation. We can conclude, however, that in the majority of cases, germline PTEN mutations lead specifically to a CS or BRR phenotype and that the phenotype of CS-like families is, for the most part, caused by unknown mechanisms.

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CURRICULUM VITAE

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Place of Birth: Republic of Singapore

Education:

1982	BA	University of Chicago, Chicago, IL (Biological Sciences with Honors)
1986	PhD	University of Chicago, Chicago, IL (Developmental Biology)
1988	MD	University of Chicago, Chicago, IL (Medicine)

Postdoctoral Training:

Internship and Residency:

1988-89	Intern, Internal Medicine, Beth Israel Hospital, Boston, MA
1989-90	Junior Assistant Resident, Internal Medicine, Beth Israel Hospital, Boston, MA
1990-91	Senior Assistant Resident, Internal Medicine, Beth Israel Hospital, Boston, MA

Fellowships:

1988-93	Clinical Fellow in Medicine, Harvard Medical School, Boston, MA
1991-94	Clinical Fellow, Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
1991-92	Clinical Fellow, Division of Medical Oncology, Brigham and Women's Hospital, Boston, MA
1992-95	Cancer Research Campaign - Dana-Farber Cancer Institute Fellow in Human Cancer Genetics, University of Cambridge, UK
1992-95	Research Fellow, Department of Pathology, University of Cambridge, UK

Licensure and Certification:

1990	Commonwealth of Massachusetts Medical Licensure, No. 72073
1991	American Board of Internal Medicine, Specialty Board Certification in General Internal Medicine, No. 135435
1992-95	Limited Registration, No. 92/3382, General Medical Council, London, UK
1997	American Board of Internal Medicine, Subspecialty Board Certification in Medical Oncology
119.	State of Ohio Medical Licensure

Academic Appointments

1994-95	Instructor in Medicine, Harvard Medical School, Boston, MA
1995-98	Assistant Professor of Medicine, Harvard Medical School, Boston, MA
1999-	Associate Professor of Medicine and Human Cancer Genetics, Ohio State University, Columbus, OH

Hospital or Affiliated Institution Appointments:

1992-95	Honorary Clinical Fellow/Senior Registrar, Clinical Cancer Genetics, Department of Clinical Genetics, Addenbrooke's Hospital, Cambridge, UK
1993-94	Honorary Clinical Status in Clinical Cancer Genetics, The Royal Marsden Hospital, London and Sutton, UK
1994-95	Honorary Consultant in Clinical Cancer Genetics, The Royal Marsden Hospital, London and Sutton, UK
1995-98	Active Staff Physician, Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA
1995-98	Associate Physician, Division of Medical Oncology, Department of Medicine, Brigham and Women's Hospital, Boston, MA
1999-	Director, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH
1999-	Member, Molecular Biology and Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, Columbus, OH

Other Professional Positions and Major Visiting Appointments

1994-95	Member, Emmanuel College, Cambridge, UK
1995-	Honorary Member, Emmanuel College, Cambridge, UK
1995	Consultant to the Molecular Genetics Laboratory, Albert Ludwigs-Universität Freiburg, Abteilung Innere Medizin IV - Nephrologie, Freiburg, Germany, July 17-19
1995-	Honorary Fellow, CRC Human Cancer Genetics Research Group, University of Cambridge, UK

Hospital and Health Care Organisation Clinical Responsibilities:

1995-98	Staff Medical Oncologist, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Boston, MA
1995-98	Staff Clinical Cancer Geneticist, Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute, Boston, MA
1995-96	Staff Medical Oncologist, Head and Neck Clinic, Dana-Farber Cancer Institute, Boston, MA
1997-98	Staff Medical Oncologist, Endocrine Cancer Clinic, Dana-Farber Partners Cancer Center, Boston, MA
1999-	Director and Attending Clinical Cancer Geneticist, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH

Major Administrative Responsibilities:

1996-99	Coordinator, Harvard Longwood Seminars in the Genetics of Cancer and Aging, Dana-Farber Partners Cancer Center, Boston, MA
1999-	Director, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH

Major Committee Assignments:

Medical School

1983-86	Interviewer for first year applicants to the Pritzker School of Medicine, University of Chicago, IL
1999-	Alternate Member, Biomedical Human Protection Committee, Ohio State University, Columbus, OH

Hospital

1995	Scientific Steering Subcommittee, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Boston, MA
1996-98	Molecular Diagnostics Committee of the Clinical Cancer Genetics Program, Dana-Farber Partners Cancer Care, Boston, MA
1996	High Risk Committee, Gastrointestinal Cancer Center, Dana-Farber Partners Cancer Care, Boston, MA
1996-98	Steering Committee, Endocrine Cancer Clinic, Dana-Farber Partners Cancer Center, Boston, MA
1997-98	Steering Committee, Gastrointestinal Cancer Center, Dana-Farber Partners Cancer Center, Boston, MA
1997-98	Human Cancer Genetics Working Group, Dana-Farber Partners Cancer Center, Boston, MA
1999-	Clinical Trials Office Steering Committee, James Cancer Hospital and Solove Research Institute and Comprehensive Cancer Center, Ohio State University, Columbus, OH
1999-	Clinical Scientific Research Committee, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH

National

1996-	Reviewer, Department of Veterans Affairs Merit Review Applications
1997-98	Reviewer and Expert Consultant, American Society of Clinical Oncology Task Force on Cancer Genetics Education
1998-	Reviewer, Molecular Biology 3 Study Section, Department of Defence US Army Research Medical and Material Command Breast Cancer Research Program
1999	Reviewer, Susan G. Komen Breast Cancer Research Foundation Grants
1999	Site Visit Team Member, Quadriannual Site Visit, National Insitute of Child Health and Development, Developmental Endocrinology Branch
1999	Reviewer, Cancer Genetics Section, American Society of Human Genetics Annual Meeting Abstracts
1999-	National Comprehensive Cancer Network (NCCN) Guidelines Panel Member: Genetics/Familial High Risk Screening Guidelines

International

1994-	Coordinator and co-chair, International *RET* Mutation Consortium
1994-	Coordinator and chair, International Cowden Syndrome Consortium
1995-98	International Review Board, Dutch Cancer Society
1997	Ad Hoc Review Committee, Programme Project Grant, National Cancer Institute of Canada

1997-	Peer Review Panel, Project Grants, Comitato Promotore Telethon, Italy
1997-	Reviewer, Project Grants and Clinical Research Fellowships, Cancer Research Campaign, London, UK
1997-	Reviewer and Full Member, National Cancer Institute of Canada, Panel J: Pathology, Tumor Markers, Molecular Epidemiology and Clinical Correlative Studies, Toronto, ON
1998-	Ad Hoc External Reviewer, Italian Association for Cancer Research
1998-	Member, Steering Committee, Breast Cancer Information Core (BIC)
1999-	Member, International Scientific Committee, 8th International Workshop on Multiple Endocrine Neoplasia, Jerusalem, Israel, May 2001

Professional Societies and Colleges:

1982-	Phi Beta Kappa, Member
1982-87	Sigma Xi, Associate Member
1982-88	American Medical Students' Association, Member
1982-88	American Medical Association, Member
1982-89	American Medical Women's Association, Member
1984-88	American Association for the Advancement of Science, Member
1984-89	New York Academy of Sciences, Member
1987-	Sigma Xi, Member
1988-	Alpha Omega Alpha, Member
1989-92	American College of Physicians, Associate
1990-98	Massachusetts Medical Society, Member
1992-99	American College of Physicians, Member
1995-	New York Academy of Sciences, Member
1996-	American Society of Clinical Oncology, Member
1996-	American Society of Human Genetics, Member
1998-	American Association for Cancer Research, Member
1999-	American College of Physicians, Fellow

Editorial Boards:

Editorial Boards:

1998-	Journal of Medical Genetics, North American Editor
1998-	Journal of Medical Genetics, Associate Editor for Cancer Genetics
1998-	Journal of Endocrine Genetics, Editorial Board Member

Ad hoc Reviewer for:

1998-	American Journal of Human Genetics
1997-	American Journal of Pathology
1997	American Journal of Surgical Pathology
1999-	BioTechniques
1997-	Blood
1998-	British Journal of Cancer
1998-	Cancer
1996	Cancer Epidemiology, Biomarkers and Prevention
1997-	Cancer Research

1997-	Carcinogenesis
1998-	Clinical Cancer Research
1995-	Clinical Endocrinology
1995-	Clinical Genetics
1996-	European Journal of Endocrinology
1997-	European Journal of Human Genetics
1997-	Experimental Cell Research
1996-	Gastroenterology
1995-	Genes, Chromosomes and Cancer
1998-	Genomics
1997-	Human Genetics
1994-	Human Molecular Genetics
1994-	Human Mutation
1998-	International Journal of Cancer
1996-	Journal of the American Medical Association
1995-	Journal of Clinical Endocrinology and Metabolism
1999-	Journal of Experimental Medicine
1999-	Journal of Clinical Investigation
1995-	Journal of Clinical Oncology
1994-98	Journal of Medical Genetics
1998-	Journal of the National Cancer Institute
1996	Mutation Research
1995-	Nature Genetics
1996-	New England Journal of Medicine
1995-	Oncogene
1997-	Proceedings of the National Academy of Sciences, USA

Awards and Honors:

1978-82	Dean's List, College, University of Chicago, IL
1981	Edmondson Summer Research Fellowship, University of Chicago, IL
1981-82	Yim Chan Merit Scholarship, University of Chicago, IL
1982	Graduation with Divisional and Collegiate Honors, University of Chicago, IL
1982	Phi Beta Kappa
1982	Sigma Xi, Associate Membership
1982	Sigma Xi Science Prize Competition, Honorable Mention, University of Chicago, IL
1982	Sigma Xi Certificate of Merit for Excellence in Undergraduate Scientific Research, University of Chicago, IL
1982-83	Dean's Letter of Commendation for Excellence in Gross Anatomy and Microbiology, Pritzker School of Medicine, University of Chicago, IL
1982-84	Far East Scholarship, Pritzker School of Medicine, University of Chicago, IL
1983	National Institutes of Health Summer Research Fellowship, Pritzker School of Medicine, University of Chicago, IL
1984-86	American Heart Association - Borg-Warner Medical Student Research Fellowship, University of Chicago, IL
1987	Sigma Xi, promotion to Full Membership
1988	Alpha Omega Alpha
1990	Nomination for Chief Residency, Department of Medicine, Beth Israel Hospital, Boston, for 1992-93 (Position Declined)

1990	Nomination for the National Institutes of Health-Upjohn Medical Residents Research Award
1991	Upjohn Travel Award to the Meeting of the American Association for Cancer Research, Houston, TX
1992	Johanna Wood Fellowship, Dana-Farber Cancer Institute, Boston, MA
1992-95	Cancer Research Campaign - Dana-Farber Cancer Institute Fellowship in Human Cancer Genetics, University of Cambridge, U.K.
1995-97	Lucille P. Markey Charitable Trust Young Scientist Award
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1996	Patterson Fellowship, Dana-Farber Cancer Institute, Boston, MA
1997-99	Barr Investigatorship, Dana-Farber Cancer Institute, Boston, MA
1999	International Scientific Committee, 8th International Workshop on Multiple Endocrine Neoplasia, Jerusalem, Israel, May, 2001

Laboratory and Clinical Investigator Track

A. Report of Research

1. Major research interests:

1. Cancer Genetics
2. Molecular Epidemiology of Cancer
3. Second Malignancies in Retinoblastoma Patients
4. Genetics of Multiple Endocrine Neoplasia Type 2 and Related Cancers
5. Familial Gastrointestinal Cancers
6. Cowden Syndrome and Related Cancers
7. Inherited Hamartoma-Neoplasia Syndromes

2. Narrative description of research

The broad thrust of my laboratory involves the utilisation of DNA-based methods to identify and characterise genes which cause susceptibility to inherited cancer syndromes, to determine their role in sporadic carcinogenesis and to perform molecular epidemiologic analyses as they might relate to future clinical applications. Upon this framework, we are examining the genetics of two inherited thyroid cancer syndromes, Cowden syndrome (nonmedullary thyroid cancer) and MEN 2 (medullary thyroid cancer), and related sporadic cancers. Hence, the genetics of susceptibility gene *PTEN*, encoding a dual specificity phosphatasw on 10q23.3, is being examined in Cowden syndrome and other inherited hamartoma syndromes as well as populations of isolated breast and thyroid cancer cases. Somatic genetics of *PTEN* is being pursued in a range of sporadic cancers including sporadic counterpart Cowden component tumors, breast, thyroid and endometrial carcinomas. Gene-gene interactions and gene-environment interactions are beginning to be explored. Biochemical, cellular and functional studies are beginning to be performed in our laboratory as well as in collaboration with a number of laboratories locally, nationally and internationally. The genetics of the *RET* proto-oncogene are pursued for clinical translational purposes for MEN 2 and sporadic neuroendocrine tumors. Towards those ends, genotype-phenotype analyses and genotype-prognosis analyses are being performed. Examination of common low penetrance variants in sporadic medullary thyroid carcinoma is also being pursued in the hope of identifying common alleles for predisposition in sporadic neuroendocrine tumors.

Recent efforts in my laboratory have focused on the role of the nuclear receptor transcription factor PPARγ in sporadic carcinogenesis. Troglitazone (Rezulin™), which is a specific synthetic ligand for PPARγ, is an oral hypoglemic agent used by over 1.6 million Americans. So, our work may have broad implications not only for examining the pathogenesis of common cancers but may impact public health as well. This avenue of investigation also promises direct translation into clinical oncologic practice.

3. Research funding information:

1981	Edmondson Summer Research Fellowship, University of Chicago (Advisor: Edward D. Garber)	PI
1978-82	Yim Chan Merit Scholarship, University of Chicago, IL	
1984-86	American Heart Association Borg-Warner Medical Student Research Fellowship, University of Chicago Pritzker School of Medicine, IL	PI
1992-95	Cancer Research Campaign [CRC] Dana-Farber Fellowship	PI

	Integrated fellowship in clinical cancer genetics and molecular cancer genetics at the University of Cambridge, UK (Advisor: Bruce A. J. Ponder)	
1995-97	New Investigator Award, Charles A. Dana Foundation	
1995-97	New Investigator Award, Markey Charitable Trust	
1995-98	Lawrence and Susan Marx Investigatorship in Human Cancer Genetics	PI
1996	Patterson Fellowship	PI
1996-98	Harvard Nathan Shock Center Award for the Basic Biology of Aging, NIA State of the art resource core for two dimensional gene scanning	
1996-99	Barr Investigatorship Human cancer genetics research	PI
1997-98	Women's Cancer Program Grant, Dana-Farber Partners Cancer Center Development of a rapid multi-gene test for hereditary breast cancer	PI
1997-99	American Cancer Society (National) Research Project Grant Isolation and characterisation of Cowden syndrome gene	PI
1997-1999	DFG Training Fellowship (Germany) Trainee PI: Oliver Gimm, MD Novel mutations and low penetrance alleles in the *RET* proto-oncogene in multiple endocrine neoplasia type 2 and sporadic medullary thyroid carcinoma	Mentor
1997-2000	Susan G. Komen Breast Cancer Foundation Postdoctoral Fellowship Trainee: Patricia L M Dahia, MD, PhD Role of Cowden susceptibility gene in breast cancer	PI
1998	Breast Cancer Research Award, Massachusetts Department of Public Health *PTEN*, the Cowden disease gene, in patients and families with breast cancer and thyroid disease	PI
1998-99	ASCO Young Investigator Award Prognostic markers for progression of esophageal adenocarcinoma Trainee PI: Matthew H. Kulke, MD	Mentor
1998-1999	Concert for the Cure Breast Cancer Research Award Genetics of *PTEN* in Cowden syndrome and unselected breast cancer patients	PI
1999	Ohio State University Seed Grant Mapping the susceptibility gene for hereditary and sporadic Barrett esophagus and esophageal adenocarcinoma	PI
1998-2001	Department of Defence US Army Breast Cancer Research Program Genetics of *PTEN* in different forms of hereditary breast cancer	PI
1998-2001	American Cancer Society (National) Research Project Grant Genetics of *PTEN* in Cowden syndrome and sporadic breast cancer	PI

1999-2002	National Institutes of Health Workstatement (RFP) A phase 2 study of a selective estrogen receptor modulator (LY353381) vs. Tamoxifen vs. placebo in premenopausal women with an increased risk for breast cancer
1999-2001	Mary Kay Ash Charitable Foundation Grant PI Genetic and functional analysis of PPAR-gamma as a novel tumor suppressor locus in sporadic breast carcinoma

B. Report of Teaching

Local Contributions

Medical School / School of Public Health

1985	Medical Genetics, Teaching Assistant for 100-110 second year medical students, University of Chicago Pritzker School of Medicine (Contact 5 hr/wk, Prep 5 hr/wk)
1996-98	Molecular Epidemiology, Guest Lecturer for 30-50 medical, dental and graduate students, medical fellows and instructors, Harvard School of Public Health (Contact 1-2 hr, Prep 2 hr)
1997	HMS211A Graduate Course in Biochemistry and Cell Biology, invited lecture on inherited cancer syndromes for 20 graduate, dental and medical students, Harvard Medical School, Boston: (Contact 1.5 hr, Prep 2 hr)
1998	Harvard Medical School Course in Genetics, Embryology and Reproduction, Tutor for group of 7-10 medical students (Contact 40 hr, Prep 20 hr)

Graduate Medical Course/Seminar/Invited Teaching Presentation

1991	Grand Rounds, Beth Israel Hospital, Boston: Causes of late mortality in retinoblastoma patients, invited speaker (Contact 20 min, Prep 3 hr)
1994	Department of Medicine Seminar Series, University of Cambridge School of Clinical Medicine: The many faces of *RET*, invited lecture for 50 housestaff and faculty of the Clinical School (Contact 1 hr, Prep 2 hr)
1996	Seminars in Medicine of the Beth Israel Hospital: From bench to bedside: the *RET* proto-oncogene in multiple endocrine neoplasia, invited lecture for 30-60 faculty and trainees from the Boston area (Contact 1.5 hr, Prep 3 hr)
1996	Harvard Medical School Department of Genetics Seminar: The polygenic etiology of Hirschsprung disease, invited speaker for 20-25 clinical genetics fellows, postdoctoral fellows and genetics faculty (Contact 1 hr, Prep 2 hr)
1997	Brigham and Women's Hospital Specialty Lecture for Medical Housestaff: Genetics of endocrine tumors, invited speaker for 50-60 medical housestaff (Contact 1 hr, Prep 1 hr)
1997	Massachusetts Cancer Center Seminar, Charlestown, MA: *RET*, *GDNF* and *GDNFR-*α in MEN 2, invited speaker for 30-50 PIs, postdoctoral fellows and graduate students (Contact 1.5 hr, Prep 2 hr)
1997	GI Grand Rounds, Massachusetts General Hospital: Molecular genetics of Hirschsprung disease for 15-25 GI fellows and faculty (Contact 1 hr, Prep 2 hr)
1997	Women's Cancer Program, Dana-Farber Partners Cancer Center, Boston: Identification of the Cowden syndrome susceptibility gene, invited speaker for 20-30 multidisciplinary faculty, clinical fellows, housestaff, postdoctoral fellows, graduate students (Contact 1 hr, Prep 1 hr)
1997	Breast Center Basic Biology Seminar, Dana-Farber Partners Cancer Center, Boston: Identification of the Cowden syndrome gene, a multipurpose gene which predisposes to breast and thyroid cancers, invited speaker for 40-60 multidisciplinary faculty, fellows and housestaff (Contact 1 hr, Prep 1 hr)
1997	Harvard-Longwood Seminars in the Genetics of Cancer and Aging, Boston: *PTEN* in inherited hamartoma-cancer syndromes: one gene-many syndromes? Invited speaker for 50-70 clinical and basic science faculty, postdoctoral fellows, clinical fellows, and graduate students from the Harvard Longwood area (Contact 1 hr, Prep 1 hr)

1997 Massachusetts General Hospital Cancer Center Grand Rounds, Boston: *PTEN* in Cowden syndrome and sporadic breast and thyroid cancers (Contact 1 hr, Prep 1 hr)

1999 Ohio State University Human Cancer Genetics Program Seminar, Columbus, OH: *PTEN* and the great imitator: Cowden syndrome (Contact 1 hr, Prep 1 hr)

Continuing Medical Education Course

1997 Cancer Genetics for Office Practice: Genetics of thyroid cancer in everyday practice, faculty (Contact 3 hr, Prep 1 hr)

1997 American College of Surgeons, Massachusetts Chapter, Waltham: Genetics of colorectal tumors, faculty (Contact 2 hr, prep 1 hr)

1998 Massachusetts Eye and Ear Infirmary and Harvard Medical School Course on Thyroid and Parathyroid Tumors: *RET* and medullary thyroid carcinoma, faculty (Contact 30 min, prep 20 min)

Advisory and Supervisory Responsibilities

1988-89 Teaching and supervision of Harvard medical students during clinical clerkship, Beth Israel Hospital, 1 medical student per rotation (200 hr/yr)

1989-91 Teaching and supervision of Harvard medical students during clinical clerkship and medical interns, Beth Israel Hospital, 2-4 interns +/- 1 medical student per rotation (2000 hr/yr)

1991-92 Teaching and supervision of medical students, and medical housestaff from Brigham and Women's Hospital and Beth Israel Hospital, 3-8 housestaff +/- 1 medical student per month (500 hr/yr)

1993-95 Teaching and supervision of technicians, students and junior postdoctoral fellows, CRC Human Cancer Genetics Research Group, Department of Pathology, University of Cambridge, 2 technicians, 0-3 medical/graduate students and 0-1 junior postdoctoral fellow (20 hr/wk)

1995- Teaching and supervision of postdoctoral fellows, students and technicians working in my laboratory, 2-6 postdoctoral fellows, 0-1 medical students, 1-3 technicians (15 hr/wk)

1996-98 Teaching and supervision of medical oncology and genetics fellows and genetics counsellors, Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute (3-5 hr/wk)

1996-98 Clinic Attending for medical oncology fellows, Dana-Farber Cancer Institute, 1-6 fellows per session (5-10 hr/mth)

1999- Direction and administration of the Clinical Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University: 1.5-2 MD attending clinical cancer geneticists, 0-1 oncology fellow, 0-1 medical resident, 3-4 cancer genetics counselors, 0-1 research assistant, 1 data manager and 2 executive support associates (20 hr/wk)

Laboratory-Based Trainees

<u>Postdoctoral Trainees</u>

Debbie J. Marsh, PhD 1996-99
Project: Genetics of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome
Current Position: Lecturer, Dept of Medicine, University of Sydney School of Medicine, Sydney, Australia

Matthew H. Kulke, MD 1997-99

Project: Molecular epidemiology and prognostic markers in sporadic gastrointestinal cancers
Current Position: Instructor in Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Patricia L.M. Dahia, MD, PhD 1997-
Project: Somatic genetics and biochemical expression of *PTEN* in sporadic tumors
Current Position: Postdoctoral Senior Research Associate, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Instructor in Medicine, Harvard Medical School

Oliver Gimm, MD 1997-
Project: Genetics of neuroendocrine tumors
Current Position: DFG Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Aurel Perren, MD 1998
Project: Immunocytochemistry of PTEN in sporadic tumors of the breast and thyroid
Current Position: Resident in Pathology, University of Zürich School of Medicine, Zürich, Switzerland

Jen Jen Yeh, MD 1998-99
Project: Somatic genetics of non-medullary thyroid carcinomas and the role of the mitochondrial genome
Current Position: Postdoctoral Research Fellow, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Liang-Ping Weng, MD, MS 1998-
Project: Biochemistry and cell biology of *PTEN* in breast and thyroid carcinogenesis
Current Position: Research Scientist, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Xiao-Ping Zhou, MD, PhD 1998-
Project: Genetics of central nervous system tumors
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Ravshan Burikhanov, PhD 1999-
Project: Cell biology of RET, PTEN and PPARgamma in thyroid cancer models
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University , Columbus, OH

Keisuke Kurose, MD, PhD 1999-
Project: Genetics of PTEN and PPARgamma in gynecologic cancers
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University Columbus, OH

<u>Student Trainees</u>

Antje Gössling 1996
Project: Genetics of GDNF and GFRα-1 in central nervous system tumors
Current Position: Resident in Clinical Genetics, Faculty of Medicine, University of Türbingen School of Medicine, Germany

Eva-Maria Dürr 1998
Project: Genetics of *CUL2* and *VBP-1* in phaeochromocytomas
Current Position: Senior Medical Student, University of Bonn School of Medicine, Germany

Ying Huang 1999-
Project: Mapping the susceptibility gene for familial nonmedullary thyroid cancer
Role: PhD thesis committee member (Albert de la Chapelle, MD, PhD, Advisor and Chair)

Junior Faculty Mentored
Matthew H. Kulke, MD Instructor in Medicine, Dana-Farber Cancer Institute
ASCO Young Investigator Award 1998-99

Kornelia Polyak, MD, PhD Assistant Professor of Medicine, Dana-Farber Cancer Institute
ASCO Career Development Award 1999-2003

Patricia L M Dahia, MD, PhD Instructor in Medicine, Dana-Farber Cancer Institute 1999-

Liang-Ping Weng, MD, MS Research Scientist, Ohio State University 1999-

Leadership Role

1995-99	Director, Harvard Longwood Seminars in the Genetics of Cancer and Aging, organisation and coordination of seminar topic and speakers, invitation of speakers, and public relations for the seminar (CME 1 course)
1999-	Director, Clinical Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University

Regional, National and International Contributions (Invited Presentations)

1993	Lancet Grand Round: Familial Cancer Syndromes. Case Presentations and Multiple Endocrine Neoplasia Type 2A, Royal Marsden Hospital, Sutton
1993	ICRF Department of Medical Oncology Seminar, St. Bartholomew's Hospital, London: The multiple endocrine neoplasia type 2 syndromes
1994	Faculty, March of Dimes 25th Clinical Genetics Conference, Orlando, FL, USA Symposium in Genetics and Development: The molecular genetics of multiple endocrine neoplasia type 2
1994	Arbeitsgemeinschaft für Gynäkologische Onkologie, Vienna, Austria: The familial and genetic risks of ovarian cancer
1994	Postgraduate Training Course in Endocrinology: Multiple Endocrine Neoplasia Type 2. British Society for Endocrinology, St. Mary's Hospital, London, UK
1994	Symposium on Genotype-Phenotype Correlations, British Medical Genetics Conference, York, UK: Mutations of the *RET* proto-oncogene in the multiple endocrine neoplasia type 2 syndromes and Hirschsprung disease
1995	Case Presentation Conference, Department of Medical Genetics, BC Children's Hospital, University of British Columbia, Vancouver: The role of the *RET* proto-oncogene in the multiple endocrine neoplasia type 2 syndromes and Hirschsprung disease
1995	Meeting of the Clinical Molecular Genetics Society, Selwyn College, Cambridge: Mutational analysis of the *RET* proto-oncogene in MEN 2

1995	Department of Internal Medicine IV - Nephrology Special Seminar, Albert Ludwigs University of Freiburg, Germany: Phaeochromocytoma and multiple endocrine neoplasia type 2: molecular genetic analysis
1995	EORTC Thyroid Group Meeting, London, UK: Germline mutations in the *RET* proto-oncogene in the multiple endocrine neoplasia type 2 syndromes
1995	Wessex Regional Genetics Laboratory Seminar, Salisbury, UK: The many faces of *RET*: multiple endocrine neoplasia type 2 and Hirschsprung disease
1996	Journées Internationales H P Klotz d'Endocrinologie Clinique, Paris, France: *RET* mutations in multiple endocrine neoplasia type 2 and sporadic medullary thyroid carcinoma
1996	Special Seminar, Institut Curie, Paris, France: Mapping of the Cowden disease susceptibility gene: clue to *BRCA3*?
1996	Medical Genetics Seminar, Institut Necker, Hopital des Enfants-Malades, Paris, France: Mutations in the *RET* proto-oncogene in MEN 2 and Hirschsprung disease
1996	Department of Endocrinology Seminar, King's College Hospital School of Medicine, London, UK: *RET* proto-oncogene in MEN 2 and sporadic MTC
1996	Department of Endocrinology Seminar, St. Bartholomew's Hospital, London, UK: Localisation of the gene for Cowden disease: another breast cancer susceptiblity gene?
1996	Special Seminar, Department of Medical Genetics, Queen's University, Kingston, ON: Cowden syndrome
1997	Université Claude Bernard Lyon I, Lyon, France: External examiner, PhD thesis committee (PhD Candidate: Isabelle Schuffenecker)
1997	Special Seminar, International Agency for Research on Cancer, Lyon, France: Molecular genetics of Cowden syndrome
1997	Special Seminar, Cancer Institute of New Jersey, New Brunswick, NJ: *PTEN* in Cowden syndrome
1997	31st Patterson Symposium: Li-Fraumeni syndrome, Manchester, UK: Two-dimensional gene scanning for rapid *p53* mutation detection
1997	IV International Thyroid and Neuroendocrine Cancer Workshop, Sicily, Italy: Genotype-phenotype correlations in MEN 2 and genotype-prognosis studies in sporadic medullary thyroid carcinoma
1998	Special Seminar, Fox Chase Cancer Center, Philadelphia: *PTEN*, encoding a dual specificity phosphatase, in inherited hamartoma-tumor syndromes
1998	Endocrine Grand Rounds, Mt. Sinai Medical Center, NY: The *RET* proto-oncogene in inherited and sporadic medullary thyroid carcinoma
1998	Special Seminar, Human Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, Columbus, OH: The paradox of the *RET* proto-oncogene: multiple endocrine neoplasia and Hirschsprung disease
1998	Special Seminar, Human Cancer Genetics Program, MD Anderson Cancer Center, Houston, TX: *PTEN* in inherited hamartoma-tumour syndromes
1998	Invited Lecture, First International Lentigenosis Meeting, National Institutes of Health, Bethesda, MD: *PTEN*, Cowden syndrome and Bannayan-Ruvalcaba-Riley syndrome
1998	Invited Symposium Lecture, Fourth European Congress of Endocrinology, Seville, Spain: *RET* and *PTEN* mutations in sporadic thyroid tumours
1998	Invited Lecture, ASCO Continuing Medical Education Course "Cancer Genetics in Office Practice," Princeton, NJ: Genetics of colorectal cancer
1998	Breast Cancer Research Centre, Vancouver, BC: *PTEN* and its role in breast tumourigenesis in Cowden syndrome

1998	Invited Lecture, 54th Recent Progress in Hormone Research, Skamania Lodge, Stevenson, WA: *PTEN*, encoding a phosphatase, in hereditary and sporadic nonmedullary thyroid tumors
1998	Invited Lecture, Gordon Research Conference DNA Alterations in Transformed Cells: New insights into the molecular genetics of cancer, Colby-Sawyer College, NH: *PTEN* mutations in two inherited hamartoma-cancer syndromes and sporadic tumors
1998	Invited Lecture, International Congress on Hereditary Cancer Diseases, Düsseldorf, Germany: Cowden syndrome: update on genetic mechanisms and clinical features
1998	Grand Rounds, University of Michigan Cancer Center, Ann Arbor, MI: The yin and yang of inherited thyroid cancer
1998	Invited Lecture, American Psychological Association Conference on Behavioral Science and Genetics, Tyson's Corner, VA: Genetic testing: from technology to treatment
1998	Karolinska Institute, Stockholm, Sweden: Faculty Opponent for PhD Thesis Defence (PhD Candidate: Filip Farnebo)
1999	Grand Rounds, NIDDK, NIH, Bethesda, MD: Genetic and epigenetic *PTEN* alterations in inherited and sporadic neoplasia
1999	Invited Lectures, NIH-sponsored Phakomatosis Revisited Workshop Rockville, MD: Hamartoses; Cowden syndrome and *PTEN*
1999	Invited Lecture, ASCO Train the Trainer Update: Bringing Cancer Genetics to Office Practice, New Orleans, LA: Molecular diagnosis of the inherited harmatoma tumor syndromes
1999	Medicine Grand Rounds, Rush Medical School, Chicago, IL: Molecular genetics in office practice: *RET* proto-oncogene mutations in multiple endocrine neoplasia type 2
1999	Molecular Medicine Seminar, University of Toronto, Canada: Genetics of *PTEN* in inherited and sporadic cancers
1999	Invited Symposium Lecture, American Gastroenterological Association, Orlando, FL: Feast or famine: *RET* proto-oncogene in intestinal ganglioneuromatosis and Hirschsprung disease
1999	Invited Plenary Lecture, Seventh International Workshop on Multiple Endocrine Neoplasia, Gubbio, Italy: MEN 2 and the practice of molecular oncology
1999	Invited Plenary Lecture, Seventh International Workshop on Multiple Endocrine Neoplasia, Gubbio, Italy: The role of *PTEN* in Cowden syndrome and multiple sporadic cancers

C. Short Report of Clinical Activities

Description of Clinical Practice: Clinical cancer genetics; medical oncology, especially inherited hamartoma tumor syndromes, and endocrine tumors in a teaching hospital setting.

Patient Load: 20% effort in the practice of clinical cancer genetics. Patients/families seen in cancer genetics clinic are usually complex and labor intensive.

Clinical Contributions: When we and other groups discovered that germline mutations in the *RET* proto-oncogene are associated with MEN 2, clinical diagnostic testing became available within 6 months of our publication. Since then, our work as well as others' work have bourne out initial data, such that *RET* testing has now become the clinical standard of care in MEN 2 and all cases of medullary thyroid cancer. Mutation status is important in these entities because it alters clinical

management for the patient and his/her family. I have also worked with at least one CLIA-certified laboratory to ensure quality control and have worked with at least one third party insurer so that *RET* testing is covered 100%.

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